Dr. Folkman's War: Angiogenesis and the Struggle to Defeat Cancer

By Robert Cooke

Random House, 365 pp, $25.95
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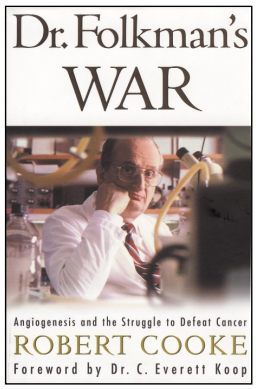
The life and work of Judah Folkman make a fascinating story. There is an old saying to the effect that truth is like daylight shining behind a curtain which has many pinholes—how much you see doesn't depend on which hole you decide to look through, but on how close to the curtain you get your eye. Judah Folkman, in a research career spanning the last three decades, has clearly got very close to the curtain indeed. Extraordinarily, he arrived in cancer research after starting in a totally different area. The research that eventually moved towards angiogenesis actually began as a project investigating the damage sustained by erythrocytes as they circulated through a prototype heart-lung machine. This was perhaps a rather unpromising pinhole to start peering through, but this book meticulously chronicles and clearly explains every step from that project, to his current research which has far-reaching implications for the way cancers are treated. Folkman wanted to find out why natural blood vessels caused less damage than metal tubes, and to do that he needed a way of looking at blood vessels. That got him interested in what makes blood vessels grow and what stops them from growing, and by that time—from what we learn of his personality—his attention was fully engaged.



At times the story reads almost like science fiction, being somewhat reminiscent of Kurt Vonnegut's creation Felix Hoenikker: the physicist who invents "ice-9" (a form of ice that is solid at room temperature) because he wants to help soldiers walk through mud, and freezing the mud seems a good solution. Folkman was clearly capable of that type of thinking and he showed, even early in his career, a rare ability to back up his thoughts and ideas with the dogged persistence to put in the hours, months and years to get a reliable answer.

Folkman's research into the mechanisms involved in tumor-induced angiogenesis has changed many fundamental aspects of the way we think about tumor growth, and ways in which that growth might be controlled. Perhaps it was inevitable that his ideas, running counter to orthodox thinking, should at first have been dismissed. But history has changed prevailing attitudes. Folkman's work has in many respects now filled the breach created by the failure of high-dose chemotherapy (with autologous marrow or stem-cell support) to cure most common solid tumors. During the 1980s and most of the 1990s when eradication of every last tumor stem-cell seemed the only way to prolong patient survival, it was not surprising that so few people were genuinely interested in tumor vasculature. Now that 'more-is-better' is no longer inviolable dogma, the world is turning its attention to Folkman's suggestion that tumor vasculature might be a far more suitable target for therapy, which might need to be administered virtually continuously rather than as periodic and sometimes highly toxic doses.

What makes this book even more interesting for researchers and clinicians alike is the degree of detail, including the naming of names. Robert Cooke, a well-known science journalist, gives the reader a blow-by-blow account of the research projects themselves and of the accompanying difficulties in grant funding, publication and partnerships with pharmaceutical and biological manufacturers. Two things will impress any researcher who reads this. First, even a major figure like Folkman had years of rejection—when his grants were turned down and some of his colleagues treated him as a pariah. Second, partnerships between academia and industry are fraught with traps, ambushes and reverses. I found myself astounded at how Folkman was able to survive and function despite so many projects that didn't turn out as hoped, rejections from funding agencies for some that had, and tussles with the various hierarchies of academic institutions and major companies.

On top of all that, there is the small matter of public relations. The world at large first heard of Judah Folkman's work in 1998 when the *New York Times* ran a front-page headline that was only a hairsbreadth away from the 'major breakthrough' cliché. It was based on a conversation with Nobel laureate James D. Watson who had said, informally, that Folkman would cure cancer in two years. Folkman has always had a reputation—completely justified in the view of all those who have heard him lecture—for enthusiasm and clarity. But, unlike a few cancer researchers, he has always resisted far-fetched speculations and any 'all-we-need-to-do-is' proclamations, and he has been careful and thoughtful in describing the implications of his work. To someone who always put so much care and thought into his statements, the *New York Times* headline must have been like a bomb. The whole story of that episode, clearly and neatly explained in this book, is a valuable manual for any scientist trying to handle the media—and it shows that things can get out of hand even when you stick to all the rules yourself.

Regarding the future and the import of Folkman's work, it is only rarely that one can agree with blurbs on the back jacket—especially if they are headed 'advance praise'. But when MIT's Robert Weinberg says that Folkman's ideas will "one day dramatically change cancer therapy," my guess is that he is right.

Virus Dynamics: Mathematical Principles of Immunology and Virology

by Martin A. Nowak & Robert M. May

Oxford Press, 237 pp, $70.00 hardcover/$34.95 paperback
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When disciplines clash there are bound to be upheavals. Speaking of discipline, it's pretty obvious that biology is in need of a bit. Our blackboards full of circles and arrows are rather too easy metaphors. Genomics and proteomics have increased the number of variables

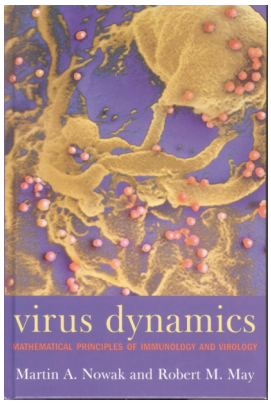
that biologists must handle. Now, try some *realpolitik*: HIV invading the immune system with antigen-specific immune responses kicking in within days, the virus preying on the very T helper cells needed to orchestrate immune response, persistence despite ferocious immune responses, and genetic variation like we've never seen before. The immune system behaves not like a well-mixed Erlenmeyer flask, but rather as a highly delocalized ensemble of clonal sites that together make the famous polyclonal response. Studying such complexity requires solid data and analyses.

Martin Nowak and Bob May have spent many years modeling the dynamics of this devastating viral infection. HIV is the Big One, measuring a 9 on the virological Richter scale. Accordingly, Nowak and May take the problem head on, making few concessions to the unwary reader—the subtitle says it all, the mathematical principles of immunology and virology. Let's put it this way, the book contains more than a handful of equations.

The modern era of viral dynamics dawned in January 1995, marked by two highly referenced papers that described the effect of powerful anti-HIV protease inhibitors in combination with extant anti-reverse transcriptase drugs. Plasma viremia was monitored by quantitative PCR, Ah! PCR again, where would we be without *Taq* polymerase? Within days of treatment, plasma viremia was knocked down 2 to 3 logs. By applying a zest of analysis, the titanic struggle between the virus and the host responses became immediately obvious. Questions such as what are the half-lives of productively infected cells and plasma viremia could now be addressed. Retrospectively it is clear that telltale signs came before, but combination therapy was the seminal advance. For the record, 'pre-modern' viral dynamics goes back to the late 1950s with the determination of half-lives of perfused virus in peripheral blood. Elegant stuff by the way.

Nowak and May cover all the major areas of interest of HIV dynamics, including the emergence of drug resistance, cell-mediated immune responses (antibodies are barely mentioned), some minutiae of quasispecies and so forth, much of which is excellent. There is a model for all seasons, and variations on a theme, which are occasionally rather sparingly explained for the biologist, follow in a rapid succession. The book is entitled viral dynamics, and included are interesting data from hepatitis B virus worthy of comment, although no allusion is made to hepatitis C virus.

The control of viremia by combination therapy or by virus-specific cytotoxic T lymphocytes (CTL) is a fascinating comparison. Using multiple drugs to hold down HIV is based on the idea that the probability of finding a mutant simultaneously resistant to three drugs is less than for two, and four drugs less than for three, and so on. If the probability is less than the inverse of HIV population size in the body, the virus can't out-maneuver the drugs. When it comes to escape from CTL, the same rule applies—tie down Gulliver with as many ropes as possible. This is so efficient a strategy that the number of convincing cases of CTL-escape is trivially small. Indeed, presenting peptide epitopes with polymorphic molecules is a marvelous way of dealing with viruses that mutate approximately one million times faster than their hosts.



How well do Nowak and May succeed? Let's back up one on viral dynamics and first look at viral quasispecies, which preceded viral dynamics. Although modeled precisely on, and of relevance to, viruses cultured *ex vivo*, the concept of viral quasispecies has not helped advance our *in vivo* understanding. Instead, it has become little more than a euphemism for genetic heterogeneity. Back to dynamics. Looking at the profusion of equations I ran, not only for cover, but to try to work out what some of the terms might correspond to in the real world of lymphoid organs. Again, the immune system is not a well-stirred Erlenmeyer flask—oligoclonal foci are legion. Antigenic stimulation of latently HIV-infected T cells occurs locally. This introduces a stochastic factor into the amplification of HIV genotypes, for expansion of the variant harbored by a cell has nothing to do with the intrinsic fitness of the variant. With an extraordinary rate of viral recombination (2–3 crossovers per cycle!), multiply infected cells, phenomenal turnover of virions and destruction of infected cells that must result in strong bottlenecking, how is genotype (fitness) conserved? Spatial discontinuities may be hard to handle mathematically, but in the case of the immune system it is a trademark.

It is not yet obvious that the modeling of HIV dynamics has profoundly changed our ideas of HIV pathogenesis. The virologists and their clinical colleagues are still the trailblazers. Yet it is easy to break along party lines, with the biologists bemoaning the complexity of the mathematics and simplifying assumptions, yet making no effort themselves to grapple with the discipline necessary to handling numerous variables. On the other side, the mathematicians may applaud the foray of their own into something as extraordinarily complex as virology. The pathologist might well remark on the exquisite spatial architecture of a lymph node, and note dryly that pathogenesis cannot be understood by the molecular biologist working with tissue culture alone. Point.

As the virological, immunological and mathematical plates become interlocked there are bound to be shocks and shake-ups. This book is a good move in the right direction. It made me think about HIV pathogenesis. Early on in the book Nowak and May make a plea for discipline and responsibility in thought. The next time I use circle and arrow metaphors I'll know who will be looking over my shoulder.